

## Pulmonary Hypertension

# Living-Donor Lobar Lung Transplantation for Pulmonary Arterial Hypertension After Failure of Epoprostenol Therapy

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<b>Objectives</b>	The aim of this study was to evaluate the long-term effects of living-donor lobar lung transplantation (LDLLT) for critically ill patients with pulmonary arterial hypertension (PAH) who failed in epoprostenol treatment.
<b>Background</b>	Although continuous epoprostenol infusion has markedly improved survival in patients with PAH, some patients do not benefit from this therapy.
<b>Methods</b>	From July 1998 to December 2003, 28 consecutive PAH patients who were treated with epoprostenol and accepted as candidates for lung transplantation were enrolled. All data were prospectively collected. As of July 2006, LDLLT was performed in 11 of those patients whose condition was deteriorating. Cadaveric lung transplantation (CLT) was performed in 2 patients. Medical treatment was continued in 15 patients.
<b>Results</b>	There was no mortality in patients receiving LDLLT during a follow-up period of 11 to 66 months (average 48 months), and all patients returned to World Health Organization functional class I. Mean pulmonary artery pressure decreased from $62 \pm 4$ mm Hg to $15 \pm 2$ mm Hg ( $p < 0.001$ ) at discharge and remained normal at 3 years. One CLT patient died of primary graft failure. Among medically treated patients, 6 patients died of disease progression. The survival rate was 100% at 5 years for patients receiving LDLLT, and 80% at 1 year, 67% at 3 years, and 53% at 5 years for patients medically treated ( $p = 0.028$ ). All living donors have returned to their previous lifestyles.
<b>Conclusions</b>	These follow-up data support the option of LDLLT in patients with PAH who would die soon otherwise. (J Am Coll Cardiol 2007;50:523–7) © 2007 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is defined as a group of disease characterized by a progressive increase in pulmonary vascular resistance (1). Epoprostenol, a potent short-acting vasodilator and inhibitor of platelet aggregation, was a therapeutic breakthrough. In long-term follow-up studies of patients with idiopathic pulmonary arterial hypertension (IPAH) receiving epoprostenol intravenous therapy, the 3-year survival ranged from 62% to 88% (2–5). The survival rate after lung transplantation was reported to be rather worse than that of patients receiving epoprostenol treatment (6). Living-donor lobar lung transplantation (LDLLT) has become an established strategy to

deal with the shortage of cadaveric donors (7,8). The aim of this study was to evaluate the long-term effects of LDLLT for critically ill patients with PAH who failed in epoprostenol treatment.

## Methods

This study included all 28 PAH (clinically diagnosed with IPAH or familial PAH) patients on epoprostenol therapy consecutively accepted as lung transplant candidates at Okayama University Hospital between July 1998 and December 2003. The lung transplant program was approved by the Ethics Committee at Okayama University Medical School. Written informed consent was obtained from all patients. The diagnosis of IPAH was established according to standard diagnostic criteria (9). Although all patients had initial diagnosis of IPAH or familial PAH, pathological findings revealed other causes of PAH in some patients as noted in the Results section. Indications for lung transplan-

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### Abbreviations and Acronyms

**BOS** = bronchiolitis obliterans syndrome  
**CLT** = cadaveric lung transplantation  
**FVC** = forced vital capacity  
**IPAH** = idiopathic pulmonary arterial hypertension  
**LDLLT** = living-donor lobar lung transplantation  
**PAH** = pulmonary arterial hypertension  
**PCH** = pulmonary capillary hemangiomatosis  
**PVOD** = pulmonary veno-occlusive disease  
**WHO** = World Health Organization

tation included World Health Organization (WHO) functional class III/IV despite optimum medical therapy and mean pulmonary artery pressure >50 mm Hg (10).

**Medical treatment.** Epoprostenol therapy was initiated at a dose of 0.5 to 1.0 ng/kg/min, and the dose was increased up to 10 to 15 ng/kg/min at discharge. After discharge, the epoprostenol dose was initially increased weekly by 0.5 to 1.0 ng/kg/min. Dose adjustments of epoprostenol were based on clinical symptoms consistent with clinical deterioration or the occurrence of adverse effects, distance walked during exercise testing, and hemodynamic measurements. Patients on the wait-

ing list for transplantation continued to receive maximum medical treatment including the oral dual endothelin receptor antagonist bosentan, which became available in June 2005.

**Cadaveric lung transplantation (CLT).** Conventional bilateral lung transplantation was performed under cardiopulmonary bypass when a cadaveric donor became available.

**LDLLT.** The policy of our program has been to limit LDLLT to critically ill patients. Right and left lower lobes from 2 healthy donors were implanted under cardiopulmonary bypass in the recipient. Relatives within the second degree or spouses have been the only donors used at our institution. When the total forced lung capacity (FVC) of the 2 grafts was >50% of the predicted FVC of the recipient, we accepted the size disparity (11).

Postoperative immunosuppression consisted of triple-drug therapy under a previously described protocol (8). Routine full postoperative assessment was performed before discharge, at 6 months, 12 months, and then annually. Right heart catheterization was performed before discharge, at 12 months, and 36 months.

**Analysis of data.** All data were collected prospectively. Three groups, patients who remained in medical treatment, patients who received CLT, and patients who received LDLLT, were compared in this study. Because CLT was performed in only 2 patients, statistical analysis was performed between the medical treatment and LDLLT groups.

All values are given as mean  $\pm$  standard error of the mean. Baseline comparisons were performed using the Pearson chi-square test (gender, inotropes), Kruskal-Wallis analysis of variance (WHO functional class), and analysis of variance (all others). Effects of LDLLT were analyzed using univariate and multivariate repeated measure of analysis. Observed survival data were reported as Kaplan-Meier estimates; the log-rank test was used to explore the significance of the difference between the groups. Comparisons of latest WHO functional class were performed using Kruskal-Wallis analysis of variance. Differences were considered significant at a probability value of <0.05.

## Results

As of July 2006, CLT was performed in 2 patients, LDLLT was performed in 11 patients, and medical treatment was continued in 15 patients.

The 28 patients' clinical characteristics when they were accepted as lung transplant candidates are shown in Table 1. Twenty-five patients (89.3%) were clinically diagnosed with IPAH. Three patients (10.7%), 1 in the CLT group and 2 in the medical treatment group, were identified as having familial PAH.

**Table 1** Baseline Clinical Characteristics of 28 PAH Patients When Accepted as Lung Transplant Candidates

	All Patients (n = 28)	Medical Treatment (n = 15)	LDLLT (n = 11)	CLT (n = 2)	p Value Medical Treatment vs. LDLLT
Women/men	20/8	10/5	9/2	1/1	0.549
Age (yrs)	24.4 $\pm$ 1.6	26.9 $\pm$ 2.1	22.4 $\pm$ 3.2	17.5 $\pm$ 1.5	0.239
Hemodynamics					
CI (l/min/m <sup>2</sup> )	2.4 $\pm$ 0.1	2.6 $\pm$ 1.6	2.1 $\pm$ 0.2	2.9 $\pm$ 0.3	0.051
PVR (dyn-s-cm <sup>-5</sup> )	1,509 $\pm$ 117	1,366 $\pm$ 150	1,782 $\pm$ 229	1,146 $\pm$ 33	0.135
mPAP (mm Hg)	61 $\pm$ 2	59 $\pm$ 3	62 $\pm$ 4	67 $\pm$ 4	0.546
mPCWP (mm Hg)	8.2 $\pm$ 0.6	8.3 $\pm$ 1.0	7.6 $\pm$ 0.9	10.0 $\pm$ 1.0	0.629
mRAP (mm Hg)	7.1 $\pm$ 0.7	6.6 $\pm$ 1.1	8.4 $\pm$ 1.1	4.0 $\pm$ 0.0	0.290
WHO functional class III/IV	18/10	11/4	5/6	2/0	0.199
Epoprostenol					
Duration (days)	340 $\pm$ 79	256 $\pm$ 104	504 $\pm$ 154	72 $\pm$ 12	0.17
Dose (ng/kg/min)	38 $\pm$ 7	25 $\pm$ 7	61 $\pm$ 14	10 $\pm$ 2	0.016
Inotropes +/-	12/16	5/10	7/4	0/2	0.136

CI = cardiac index; CLT = cadaveric lung transplantation; LDLLT = living-donor lobar lung transplantation; mPAP = mean pulmonary artery pressure; mPCWP = mean pulmonary capillary wedge pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organization.

Cardiac index was marginally lower ( $p = 0.051$ ), and the dose of epoprostenol was significantly higher ( $p = 0.016$ ) in patients who subsequently received LDLLT than in those who remained in medical treatment.

**Medical treatment.** Among the 15 patients who remained in medical treatment, 6 patients died of disease progression. Autopsy was performed in 4 patients. Two patients were diagnosed with IPAH, 1 with pulmonary capillary hemangiomatosis (PCH), and 1 with pulmonary veno-occlusive disease (PVOD).

Among the 9 survivors, 8 patients recovered to WHO functional class II and they were removed from the active list for lung transplantation. Six of them are currently treated with oral bosentan along with intravenous epoprostenol.

**CLT.** Two patients received conventional bilateral lung transplantation. One patient died of primary graft failure. The other patient is alive after 34 months.

**LDLLT.** Eleven patients received LDLLT. Seven patients received LDLLT within 2 weeks after being accepted as lung transplant candidates. Four patients waited on the list for cadaveric donors for 80 to 1,244 days, and then they received LDLLT due to their clinical deterioration from WHO functional class III to class IV or due to episodes of life-threatening events such as massive hemoptysis.

The 11 patients' clinical characteristics when they received LDLLT are shown in Table 2. Two patients (cases 3 and 7) were too sick to undergo right heart catheterization before transplantation, so pulmonary hemodynamics measured >12 months before transplant were used as preoperative data.

One pediatric patient (case 2) underwent right single lobe transplantation (12). The other 10 patients received bilateral LDLLT. The total FVC of the grafts was estimated to range from 51.4% to 103.0% (average 70.1%) of the predicted FVC of the recipient.

The major operative morbidity included lung edema requiring reintubation ( $n = 3$ ), bleeding from the chest wall requiring rethoracotomy ( $n = 2$ ), massive hemoptysis requiring extracorporeal membrane oxygenation ( $n = 1$ ), and kinking of the left pulmonary artery requiring vascular repair ( $n = 1$ ). Duration of mechanical ventilation required was  $13.4 \pm 3.6$  days, and hospital stay was  $75.8 \pm 7.9$  days. All 11 patients were discharged without oxygen inhalation therapy. There were no postoperative complications among 21 living donors.

Pathologic diagnoses of the excised lungs were IPAH in 9 patients, PCH in 1 patient (case 8), and PVOD in 1 patient (case 9).

Functional assessment is summarized in Table 3. Pulmonary hemodynamics improved dramatically at discharge and continued to be excellent at 3 years. Spirometric measurements improved gradually during the first year and exceeded preoperative values at 1 to 3 years.

Although unilateral bronchiolitis obliterans syndrome (BOS) developed in 2 pediatric recipients (cases 4 and 7), their contralateral graft was unaffected. All 11 recipients and 21 donors remained alive during the observation period.

Table 2 Baseline Characteristics of the 11 Patients Receiving LDLLT at the Time of Transplantation

Patient No.	Age (yrs)/Gender	Height (cm)	Weight (kg)	CI (l/min/m <sup>2</sup> )	PVR (dyn·s·cm <sup>-5</sup> )	mPAP (mm Hg)	mPCWP (mm Hg)	mRAP (mm Hg)	WHO Class	Epoprostenol		Inotropes
										Duration	Dose	
1	19/F	157	38.0	1.4	2,012	58	11	15	IV	1,726	160	+
2	10/M	122	20.4	2.7	1,772	59	8	9	III	737	90	+
3	27/F	160	50.8	1.5	—	53	—	10	IV	840	24	+
4	8/M	126	20.0	1.7	2,340	52	10	5	IV	281	123	+
5	13/F	147	39.7	2.2	3,282	98	6	4	IV	570	90	+
6	31/F	160	41.7	2.1	1,229	48	6	8	IV	88	140	+
7	13/F	148	35.0	1.7	2,277	67	8	6	IV	309	76	+
8	25/F	164	45.0	1.9	1,455	55	4	8	IV	1,344	50	+
9	28/F	152	33.0	1.8	2,278	66	3	10	III	115	46	—
10	43/F	156	52.8	2.5	1,229	72	12	15	IV	350	50	+
11	35/F	160	54.0	3.1	641	51	10	9	IV	1,210	127	+
Mean	22.9 ± 3.4	150 ± 4	39.1 ± 3.5	2.1 ± 0.2	1,852 ± 225	62 ± 4	7.8 ± 0.9	9.0 ± 1.1		688 ± 163	89 ± 13	

Abbreviations as in Table 1.

Table 3 Functional Assessment Before and After LDLLT

	Pretransplant (n = 11)	Post-Transplant Interval		
		2–3 Months (n = 11)	1 Year (n = 10)	3 Years (n = 9)
CI (l/min/m <sup>2</sup> )	2.1 ± 0.1	2.8 ± 0.2	3.3 ± 0.3*	3.1 ± 0.2†
PVR (dyn·s·cm <sup>−5</sup> )	1,852 ± 225	234 ± 27‡	174 ± 23‡	172 ± 24‡
mPAP (mm Hg)	62 ± 4	15 ± 2‡	16 ± 1‡	15 ± 1‡
mPCWP (mm Hg)	7.8 ± 0.9	5.3 ± 0.8	6.0 ± 0.6	7.5 ± 1.0
mRAP (mm Hg)	9.0 ± 1.1	−0.5 ± 0.7	1.5 ± 0.6	2.0 ± 0.4
FVC (ml)	2,014 ± 185	1,401 ± 100	2,073 ± 131§	2,291 ± 157§
%FVC (%)	72.9 ± 5.3	57.9 ± 3.3	78.0 ± 3.0§	81.3 ± 3.9
FEV <sub>1.0</sub> (ml)	1,517 ± 135	1,373 ± 120	1,818 ± 134§	1,902 ± 141§
FEV <sub>1.0</sub> (%)	76.0 ± 2.4	91.9 ± 2.3	87.2 ± 1.8	82.7 ± 2.2
PaO <sub>2</sub> (mm Hg)		93.6 ± 2.1	100.6 ± 3.5	97.0 ± 3.0
PaCO <sub>2</sub> (mm Hg)	33.7 ± 1.8	35.6 ± 0.6	35.7 ± 0.8	35.5 ± 1.7
6-min walk (m)		300 ± 20	457 ± 16§	518 ± 60§

\*p < 0.05 (vs. pretransplant); †p < 0.001 (vs. pretransplant); ‡p < 0.0001 (vs. pretransplant); §p < 0.0001 (vs. 2 to 3 months); ||p < 0.01 (vs. 2 to 3 months).  
 FEV<sub>1.0</sub> = forced expiratory volume in 1 s; FVC = forced vital capacity; PaCO<sub>2</sub> = arterial carbon dioxide tension; PaO<sub>2</sub> = arterial oxygen tension; other abbreviations as in Table 1.

**Comparison in survival and latest function.** At the time of final data analysis in July 2006, the mean time from the date the patient was accepted as a lung transplant candidate to final analysis for all 28 patients was 58 months (range 31 to 95 months). The mean time from LDLLT to final analysis was 48 months (range 11 to 66 months). The survival rate was 100% at 5 years for patients receiving LDLLT, whereas it was 80% at 1 year, 67% at 3 years, and 53% at 5 years for patients who remained in medical treatment (Fig. 1) (p = 0.028).

The latest patient WHO functional class is summarized in Table 4. All 11 patients receiving LDLLT are currently in class I. The functional class was significantly better in

patients receiving LDLLT than in patients who remained in medical treatment (p < 0.001).

### Discussion

Several series have demonstrated the positive impact of epoprostenol on survival in IPAH (2–5). There are now 3 classes of medications that have shown efficacy in the treatment of PAH: prostanoids (2–5), endothelin receptor antagonists (13), and phosphodiesterase-5 inhibitors (14). Because of the remarkable improvements of medical treatment for PAH during the past decade, determining the indications and timing for transplantation as a PAH treatment is a difficult challenge

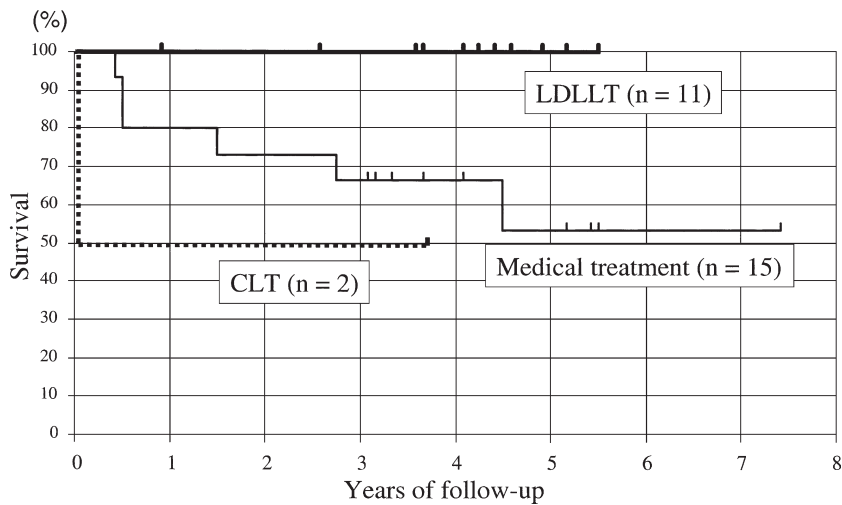


Figure 1 Kaplan-Meier Survival Curves in PAH Patients

Survival was assessed from the date of operation in patients receiving transplantation and from the date of acceptance as lung transplant candidates in patients treated medically. The survival was significantly better in patients receiving living-donor lobar lung transplantation (LDLTT) than in patients medically treated. p = 0.028, log-rank test. CLT = cadaveric lung transplantation; PAH = pulmonary arterial hypertension.

**Table 4 Latest WHO Functional Class**

Latest WHO Functional Class	Medical Treatment (n = 15)	LDLLT (n = 11)	CLT (n = 2)
Class I	0	11	1
Class II	8	0	0
Class III	1	0	0
Class IV	0	0	0
Deceased	6	0	1

p < 0.001 (medical treatment vs. LDLLT) by Kruskal-Wallis analysis of variance.  
Abbreviations as in Table 1.

knowing that the survival after CLT was reported to be rather worse than epoprostenol treatment (6).

Living-donor lobar lung transplantation was pioneered by the University of Southern California group. They originally applied this procedure almost exclusively to cystic fibrosis patients and then expanded the indications to other diagnoses including pediatric IPAH in 5 patients (7). Since January 2000, we have applied this procedure to both pediatric (12) and adult (15) patients with IPAH. Because LDLLT subjects healthy donors to a lower lobectomy procedure associated with potentially serious complications, we have accepted only critically ill IPAH patients who failed in epoprostenol therapy.

There were obvious concerns regarding whether pulmonary hypertension would develop in only 2 lobes implanted. Their mean pulmonary artery pressure decreased from  $62 \pm 4$  mm Hg to  $15 \pm 2$  mm Hg at discharge, validating the functional capacity of the 2 lobes to handle the entire cardiac output.

The major limitation to long-term survival in CLT is death due to chronic rejection (6). In our entire experience of LDLLT in 39 patients with various lung diseases, 8 patients (21%) developed BOS. Interestingly, 7 of 8 patients had unilateral BOS. The different antigenicity between 2 LDLLT grafts might explain this phenomenon. Thirty-seven of the 39 LDLLT patients (95%) are currently alive.

In the new classification of pulmonary hypertension (1), PCH and PVOD are included in a subgroup termed “PAH associated with significant venous or capillary involvement.” Their clinical presentation is generally similar to that of IPAH; however, the prognosis seems worse. Of note was that both PCH and PVOD were found in patients receiving LDLLT and also in patients on epoprostenol therapy who died while on the waiting list.

Although all data were collected prospectively, the major limitation of this study is its nonrandomized design. Nevertheless, this study suggests that LDLLT can provide better survival than medical treatment including epoprostenol. Patients receiving LDLLT seemed to have more advanced disease than patients who remained in medical treatment when they were accepted as lung transplant candidates (Table 1). All 11 patients receiving LDLLT are currently in class I during the mean follow-up period of 48 months (Table 4).

It should be also noted that 8 of 15 patients in the medical treatment group had a long-lasting benefit from epoprostenol therapy and may never require lung transplantation. Although knowledge of predictors of survival in patients with PAH is helpful, ultimately the timetable must be set by the unique situation of each patient. These follow-up data support the option of LDLLT in patients with PAH who would die soon otherwise.

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